of utilizing an abstract and the protein discussed therein. We believe the amended claims and accompanying response are in the spirit of our discussion and should place the application in condition for allowance. In the event the Examiner disagrees a courtesy call would be appreciated.

The Office Action mailed March 25, 2002, has been received and carefully considered. In this response, Applicant has amended claims 36-38, 41-42, 62, and 72. Entry of these amendments is respectfully requested. Upon entry of this response, claims 36-39, 41-42, 45-67, and 69-72 will be pending.

**Rejections under 35 U.S.C. § 112 ¶ 1**

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

On page 2, section 5, the USPTO rejected claims 36-39, 41-42, 45-47, 62, 66-67, and 69-72 under 35 U.S.C. §112 ¶ 1, as allegedly "not providing support for variants of the disclosed differentiation-inducing factor" for the reasons of record. More specifically, the USPTO states that the specification provides "no guidance as to where to obtain cells that would contain such variants of the differentiation-inducing activity, or if such variants exist, or must be obtained by the expression of synthetic polynucleotide sequences." The Applicant has amended the relevant claims to require that the respective fragment or variant "retains said differentiation-inducing activity." This functional language as discussed during the interview provides further guidance to a person skilled in the art on how to make and use the invention as claimed.

Further, as is notoriously well established under 35 U.S.C. §112 ¶ 1, "the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (*United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1986)). The factors to be considered in determining whether a disclosure would require undue experimentation include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 773 (1988). In the present case, a person skilled in the art could readily ascertain other proteins

possessing the activity of the invention, and test said proteins, fragments, or variants thereof to ascertain whether they retain the differentiation-inducing activity.

The Applicant again urges that pages 18-22 provide a comprehensive disclosure describing the physical and functional properties of the protein, preferred tissues to obtain sequences, fragments, and variants thereof, and methods of testing sequences, fragments, and variants for erythroid differentiation activity. The Applicant notes by way of example only that the specification at least on pages 2 lines 24-28 and page 3 lines 1-4, discusses the gene as "expressed in the form of different RNA species (presumably splice variants) of about 800, 1,200, 1,350, 1,750, and 2,200 bp" as exemplification of possible fragments.

The Applicant again directs the Examiner's attention to *Ex parte Mark*, where the Board of Patent Appeals particularly addressed the breadth of claims under 35 U.S.C. §112 ¶ 1 for protein sequences stating "...one skilled in the art would be able to routinely determine whether deletion or replacement of cysteine residues would result in a mutein which is within the claims." 12 U.S.P.Q.2d 1904, 1907 (1989). Similar to the present application, the Board recognized that "[o]ne skilled in the art is clearly able to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity." 12 U.S.P.Q.2d 1904, 1907 (1989). Likewise, one skilled in the art would be able to perform the work needed to determine whether fragments or variants of the claimed protein retain the differentiation-inducing activity, particularly in light of the specification.

As previously discussed in the last response and during the interview, it is now recognized routine practice for one skilled in the art to obtain a large sequence and utilize routine practices to obtain active fragments thereof. The court in *Ajinomoto Co. Inc.*, recognized that "how to identify ...genes...in the donor bacterium, how to obtain a chromosome DNA fragment, how to obtain suitable plasmids, how to isolate recipient bacterial strains, and how to perform transformation steps" are "well known to those skilled in the art." 56 U.S.P.Q.2d 1332, 1345 (Fed. Cir. 2000). Further, *Ex parte Mark*, makes clear that the ability to start with disclosed fragments and perform testing by a known method is sufficient under 35 U.S.C. §112 ¶ 1. 12 U.S.P.Q.2d 1904 (1989).

The Applicant has provided by way of example several sequences and methods for testing said sequences and fragments to see if they retain said erythroid differentiation activity and should not improperly limited to the examples.

Applicant respectfully traverses this rejection.

**Rejections under 35 U.S.C. § 102(b)**

A person shall be entitled to a patent unless –
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.

On page 3, section 6 of the Office Action the USPTO rejected claims 36-39, 45-46, 66, and 69-72 under 35 U.S.C. § 102(b) as allegedly anticipated by Dormer et al (Experimental Hematology, 1992, Vol. 20, p. 758). As was previously argued and discussed during the interview the Dormer et al. reference fails to provide adequate information to be properly used as a reference under 35 U.S.C. § 102(b) with regard to the protein described in the reference. In this regard, as an Abstract, Dormer et al. is properly cited only for that which it expressly teaches, and may not be used as a vehicle through which the teachings of the underlying article. The Board recently discussed its strong preference against the use of such Abstracts in Ex parte Jones, 62 U.S.P.Q. 2d 1206, 1208 (BPAI 2001) (A copy of this case was provided to the Examiner during the interview.). However, to further distinguish the reference the Applicant has provided a Declaration by Dr. Dormer, the first author of the reference stating, that the protein is not the same as that described in the present invention. In particular, the Declaration states that the protein described in the article as "described by others" refers to a protein described in Kajigaya *et al.* (A copy of the Kajigaya *et al.* has been provided as an attachment to the response. Additionally, please note that we have been informed there is no full article related to the abstract.)

As is evident from the Kajigaya *et al.* article the proteins are not the same. As shown in Figure 1, on page 369 the protein in Kajigaya et al. is approximately 15 kDa. The protein of the claimed invention has a molecular weight range between 10 kDa and 60 kDA, with a peak molecular range between 40 kDa to 60 kDa. Further most of the experiments in the Dörmer et al. reference were in fact done with 32D cells, a murine myeloid cell line, related to myeloid differentiations system and the observation related to erythroleukemic cells were the down regulation of *c-myb* in F4N and B8/3 cells by WEHI-3B supernatant associated with globin mRNA synthesis. Neither the finding of c-myb down regulation nor the induction of globin mRNA by Dörmer et al. synthesis sufficiently describes hemoglobin synthesis to place one of ordinary skill in the art in possession of the claimed invention.

The present invention is directed toward an isolated protein with differentiation-inducing activity on Friend Erythroleukemia cell lines comprising the induction of differentiation in Friend Erythroleukemia cell lines with hemoglobin formation; a molecular weight in the range of about 10-60 kDa as determined by gel filtration on a cross-linked allyl dextran; an expression of the corresponding mRNA in primary cells of the thymus, fetal liver, adult spleen, or bone marrow; encoded by a cDNA comprising repeat sequences of SEQ ID NOS: 6 and 7; wherein the corresponding mRNA comprises mRNA species of differing length, said mRNA species comprising; identical 3' regions corresponding to the coding region of SEQ ID NO:2; and non-identical 5' regions. To constitute anticipation, all material elements of the claim must be found in one prior art source. (In re Marshall, 577 F.2d 301, 198 USPQ 344 (CCPA 1978).

Claims 36-39, 45-46, 66, and 69-72 claim polypeptide sequences encoded by polynucleotide sequences corresponding to SEQ ID NOs: 2 and 6-10. As aptly noted by the Examiner in the previous Office Action, Dormer et al. do not disclose the polynucleotide sequences of SEQ ID NOs: 2 and 6-10. Further, the Dormer et al. reference refers to work by others but does not provide any means for determining who the others are, the exact nature of their work, or the exact nature of the protein. The Dormer et al. reference on its face fails to provide every aspect of the claimed invention. The Examiner stated that the "protein of Dormer appears to be the same protein as it is obtained from the same source and exerts the same functional activity of the claimed protein." (Emphasis Added). Even the Examiner can not determine from the reference what has been disclosed in the Dormer et al. reference. Therefore, Dormer et al. is not available as proper 35 U.S.C. § 102(b) art against claims 36-39, 45-46, 66, and 69-72.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 36-39, 45-46, 66, and 69-72 under 35 U.S.C. § 102(b). Applicant respectfully traverses this rejection.

## Conclusion

Applicant believes that incorporation of the amendments and consideration of the above remarks has placed this application in a condition for allowance. Early notification of a favorable consideration is requested.

Respectfully submitted,

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July 25, 2002 By:

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**Attachment A - Version With Markings To Show Changes Made**

36. (Four Times Amended) An isolated protein with differentiation-inducing activity on Friend Erythroleukemia cell lines comprising the following properties:

a. induction of~~s~~ differentiation in Friend Erythroleukemia cell lines with hemoglobin formation;

b. a molecular weight in the range of about 10-60 kDa as determined by gel filtration on a cross-linked allyl dextran;

c. ~~with~~ an expression of the corresponding mRNA in primary cells of the thymus, fetal liver, adult spleen, or bone marrow;

d. is encoded by a cDNA comprising repeat sequences of SEQ ID NOS: 6 and 7;

e. ~~with~~ wherein the corresponding mRNA comprises mRNA species of differing~~ent~~ length, said mRNA species comprising:

i. identical 3' regions corresponding to the coding region of SEQ ID NO:2; and

ii. ~~but different~~non-identical 5' regions.

37. (Thrice Amended) Protein according to claim 36, wherein said protein comprises at least one of the following features:

a. said protein is encoded by a corresponding mRNA which shows an *in vitro* upregulation and/or accumulation if a three day allogeneic spleen cell reaction is carried out with non-irradiated, not pretreated spleen cells of mouse strains CBA and C57B1/6;

b. having AT rich regions in the cDNA, the 3' part of which encodes the protein; or

c. inducible by a serum factor present in fetal calf serum.

38. (Twice Amended) Protein according to claim 36, wherein one or more of ~~the repeat sequences~~ SEQ ID NO~~S~~:-6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, ~~10~~ or of repeat sequences hybridizing to SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10~~these repeat sequences~~ under stringent conditions are present in the DNA encoding the protein, said stringent conditions comprising hybridization at 65°C in an aqueous solution.

41. (Thrice Amended) Protein according to claim 36, wherein said protein comprises a partial amino acid sequence encoded by a DNA hybridizing to a fragment of the cDNA or SEQ ID NO:1 or NO:2 or NO:4 under stringent conditions, wherein said fragment retains said differentiation-inducing activity.

42. (Twice Amended) Protein according to claim 36, comprising variants of said protein comprising an amino acid sequence ~~which is sufficiently similar~~ wherein said variant retains said differentiation inducing activity on friend erythroleukemia cell line ~~to that of the protein of Claim 36 so as to exhibit differentiation inducing activity on Friend erythroleukemia cell lines~~ or a fusion protein comprising said protein of Claim 36 or said variant.

62. (Twice Amended) A t~~T~~herapeutic composition comprising:

a. the protein of Claim 36, or a variant or fragment of said protein wherein said variant or fragment retains said differentiation-inducting activity; and

b. ~~comprising an amino acid sequence which is sufficiently similar to that of the protein of Claim 36 so as to exhibit differentiation inducing activity on Friend erythroleukemia cell lines together with~~a conventional carrier~~s~~ and/or excipient in an amount effective to treat diseases accompanied by impairment of differentiation inducing activity in erythropoietic cells.

72. (Four Times Amended) An isolated protein with differentiation-inducing activity on Friend erythroleukemia cell lines comprising the following properties:

a. induction of~~s~~ differentiation in Friend erythroleukemia cell lines with hemoglobin formation;

b. a molecular weight in the range of about 10-60 kDa as determined by gel filtration on a cross-linked allyl dextran;

c. ~~with an~~ expression of the corresponding mRNA in primary cells of the thymus, fetal liver, adult spleen, or bone marrow;

d. is encoded by a cDNA comprising repeat sequences of SEQ ID NOS: 6 and 7 or sequences which hybridize with said repeat sequences under stringent conditions;

e. ~~with~~ wherein the corresponding mRNA comprises mRNA species of differin~~gent~~ length, said mRNA species comprising;

i. identical 3' regions corresponding to the coding region of SEQ ID NO:2 or sequences which hybridize with said coding region under stringent conditions; and, ~~but~~

ii. non-identical ~~different~~ 5' regions,

wherein said stringent conditions comprise~~ing~~ hybridization at 65°C in an aqueous solution or at 42°C in 50% formamide and subsequent washing of the filter at 60°C in an aqueous solution having a salt concentration of 15mM NaCl and a concentration of SDS of 0.1%.